PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 09 July 1999 (09.07.99)	
International application No. PCT/US98/23496	**Applicant's or agent's file reference** 5555-501
International filing date (day/month/year) 04 November 1998 (04.11.98)	**Priority date** (day/month/year) 10 November 1997 (10.11.97)
Applicant INSEL, Paul, A. et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

18 May 1999 (18.05.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b):

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer D. Barmes
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 5555-501	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US98/23496	International filing date *(day/month/year)* 04 NOVEMBER 1998	Priority date *(day/month/year)* 10 NOVEMBER 1997
International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet.		
Applicant THE REGENTS OF THE UNIVERSITY OF CALIFORNIA		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 10 sheets.

3. This report contains indications relating to the following items:

   I ☒ Basis of the report

   II ☐ Priority

   III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability

   IV ☐ Lack of unity of invention

   V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

   VI ☐ Certain documents cited

   VII ☐ Certain defects in the international application

   VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
18 MAY 1999	18 FEBRUARY 2000
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JEFFREY FREDMAN Telephone No. (703) 308-0196

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US98/23496

I. Basis of the report

1. This report has been drawn on the basis of *(Substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments)*:

[X] the international application as originally filed.

[X] the description, pages (See Attached) , as originally filed.
pages _____ , filed with the demand.
pages _____ , filed with the letter of _____.
pages _____ , filed with the letter of _____.

[X] the claims, Nos. (See Attached) , as originally filed.
Nos. _____ , as amended under Article 19.
Nos. _____ , filed with the demand.
Nos. _____ , filed with the letter of _____.
Nos. _____ , filed with the letter of _____.

[X] the drawings, sheets/~~fig~~ (See Attached) , as originally filed.
sheets/~~fig~~ _____ , filed with the demand.
sheets/~~fig~~ _____ , filed with the letter of _____.
sheets/~~fig~~ _____ , filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

[X] the description, pages NONE.

[X] the claims, Nos. NONE.

[X] the drawings, sheets/~~fig~~ NONE.

3. [ ] This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the ~~Supplemental Box~~ Additional observations below (Rule 70.2(c)).

4. Additional observations, if necessary:

NONE

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US98/23496

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims	3-10, 13-20, 22-36	YES
	Claims	1, 2, 11, 12, 21	NO
Inventive Step (IS)	Claims	15, 19	YES
	Claims	1-14, 16-18, 20-36	NO
Industrial Applicability (IA)	Claims	1-36	YES
	Claims	NONE	NO

2. CITATIONS AND EXPLANATIONS

Claims 1, 2, 11, 12 and 21 lack novelty under PCT Article 33(2) as being anticipated by SYNAPTIC PHARMACEUTICAL CORPORATION (WO 94/08040).

SYNAPTIC PHARMACEUTICAL CORPORATION teaches a method of amplifying a segment of human 11b adrenergic receptor gene comprising the steps of: a) providing a biological sample of the subject containing nucleic acids (page 55, lines 18-24), b) amplifying a segment of the gene using oligonucleotide primers, DNA polymerase and dNTPs (page 55, lines 18-35).

SYNAPTIC PHARMACEUTICAL CORPORATION teaches oligonucleotide primer pairs for the amplification of an alpha 1b adrenergic receptor which are greater in length than 15 nucleotides, which are non-crosshybridizing, which anneal to two distinct regions about 400 nucleotides apart with melting temperatures over 50 C (page 55, lines 23-37).

Claims 1-14, 16-18, 20 and 21 lack an inventive step under PCT Article 33(3) as being obvious over SYNAPTIC PHARMACEUTICAL CORPORATION (WO 94/08040) in view of Ramarao et al (J. Biol. Chem. (1992) 267(30):21936-21945) and further in view of Emorine et al (Proc. Natl. Acad. Sci. (1987) 84:6995-6999).

SYNAPTIC PHARMACEUTICAL CORPORATION teaches a method of amplifying a segment of human 11b adrenergic receptor gene comprising the steps of: a) providing a biological sample of the subject containing nucleic acids (page 55, lines 18-24), b) amplifying a segment of the gene using oligonucleotide primers, DNA polymerase and dNTPs (page 55, lines 18-35).

SYNAPTIC PHARMACEUTICAL CORPORATION teaches oligonucleotide primer pairs for the amplification of an alpha 1b adrenergic receptor which are greater in length than 15 nucleotides, which are non-crosshybridizing, which anneal to two distinct regions about 400 nucleotides apart with melting temperatures over 50 C (page 55, lines 23-37).
(Continued on Supplemental Sheet.)

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

CLASSIFICATION:
The International Patent Classification (IPC) and/or the National classification are as listed below:
IPC(7): C07H 21/02, 21/04; C12Q 1/68; C12P 19/34 and US Cl.: 536/24.3, 24.31, 24.32, 24.33; 435/6, 91.1, 91.2, 91.21

I. BASIS OF REPORT:

This report has been drawn on the basis of the description,
pages, 1-33 and sequence listing pages 1-5, as originally filed.
pages, NONE, filed with the demand.
and additional amendments:
NONE

This report has been drawn on the basis of the claims,
numbers, 1-36, as originally filed.
numbers, NONE, as amended under Article 19.
numbers, NONE, filed with the demand.
and additional amendments:
NONE

This report has been drawn on the basis of the drawings,
sheets, 1-6, as originally filed.
sheets, NONE, filed with the demand.
and additional amendments:
NONE

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):

SYNAPTIC PHARMACEUTICAL CORPORATION further teaches methods for diagnosis of diseases related to human alpha 1 adrenergic receptors comprising nucleic acid probe techniques (page 12, lines 10-32). SYNAPTIC PHARMACEUTICAL CORPORATION expressly teaches a variety of diseases including hypertension which are related to alterations in alpha 1 adrenergic receptor activity (page 73, line 32 to page 74, line 19). SYNAPTIC PHARMACEUTICAL CORPORATION expressly teaches an oligonucleotide sequence which comprises SEQ ID NO:s 1-38. Here are the alignments, as drawn from figure 2 for SEQ ID NO: 1;

```
  Query Match           100.0%;  Score 19;  DB 22;  Length 1738;
  Best Local Similarity 100.0%;  Pred. No. 4.45e-01;
  Matches    19;  Conservative    0;  Mismatches   0;  Indels   0;  Gaps   0;

Db      31 CGGGGGAAGCAAAGTTTCA 49
           |||||||||||||||||||
Qy       1 CGGGGGAAGCAAAGTTTCA 19
```

for SEQ ID NO: 2;

```
  Query Match           100.0%;  Score 20;  DB 22;  Length 1738;
  Best Local Similarity 100.0%;  Pred. No. 8.61e-03;
  Matches    20;  Conservative    0;  Mismatches   0;  Indels   0;  Gaps   0;

Db     778 ATTCTAGTCATGTACTGCCG 797
           ||||||||||||||||||||
Cp      20 ATTCTAGTCATGTACTGCCG 1
```

for SEQ ID NO: 3;

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII


```
  Query Match           100.0%;  Score 19;  DB 22;  Length 1738;
  Best Local Similarity 100.0%;  Pred. No. 2.90e-01;
  Matches    19;  Conservative    0;  Mismatches   0;  Indels   0;  Gaps   0;

Db     662 CTCTCCTTGGGTGGAAGGA 680
           |||||||||||||||||||
Qy       1 CTCTCCTTGGGTGGAAGGA 19
```

Ramarao teaches an oligonucleotide sequence which comprises SEQ ID NO:4.
for SEQ ID NO: 4;

```
  Query Match           100.0%;  Score 20;  DB 26;  Length 2669;
  Best Local Similarity 100.0%;  Pred. No. 6.52e-02;
  Matches    20;  Conservative    0;  Mismatches   0;  Indels   0;  Gaps   0;

Db    1919 CTTGGGTTTACTGATGAGCT 1938
           ||||||||||||||||||||
Cp      20 CTTGGGTTTACTGATGAGCT 1
```

Emorine teaches an oligonucleotide sequence which comprises SEQ ID NO:5, 6 and 8.
for SEQ ID NO: 5;

```
  Query Match           100.0%;  Score 20;  DB 26;  Length 3458;
  Best Local Similarity 100.0%;  Pred. No. 2.67e-02;
  Matches    20;  Conservative    0;  Mismatches   0;  Indels   0;  Gaps   0;

Db    1161 GAATGAGGCTTCCAGGCGTC 1180
           ||||||||||||||||||||
Qy       1 GAATGAGGCTTCCAGGCGTC 20
```

for SEQ ID NO: 6;

```
  Query Match           100.0%;  Score 19;  DB 26;  Length 3458;
  Best Local Similarity 100.0%;  Pred. No. 3.40e-02;
  Matches    19;  Conservative    0;  Mismatches   0;  Indels   0;  Gaps   0;

Db    2079 CAAGACGTTAGGCATCATC 2097
           |||||||||||||||||||
Cp      19 CAAGACGTTAGGCATCATC 1
```

for SEQ ID NO: 8

```
  Query Match           100.0%;  Score 19;  DB 26;  Length 3458;
  Best Local Similarity 100.0%;  Pred. No. 3.40e-02;
  Matches    19;  Conservative    0;  Mismatches   0;  Indels   0;  Gaps   0;


Cp       1    tcctctaggactaaagctc 19
              ||||||||||||||||||||
Db: 2769      tcctctaggactaaagctc 2751
```

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to select human alpha 1b adrenergic primers from the sequences of Emorine or Ramarao or SYNAPTIC PHARMACEUTICAL CORPORATION since SYNAPTIC

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

PHARMACEUTICAL CORPORATION states "This invention provides a nucleic acid probe comprising a nucleic acid probe molecule of at least 15 nucleotides capable of specifically hybridizing with a sequence included within the sequence of a nucleic acid molecule encoded by a human alpha 1b receptor (page 5, lines 16-21)". An ordinary practitioner, given these sequences would have recognized that the claimed primers simply represent structural homologs, which are suggested by the prior art in a gene designated as useful for PCR amplification, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are prima facie obvious over the cited references in the absence of secondary considerations. Further, selection of the specific oligonucleotides from a larger known gene sequence represents routine optimization with regard to sequence, length and compositions, which routine optimization parameters are explicitly recognized in the cited prior art of Bard. Routine optimization is not considered inventive and no evidence has been presented that the probe selection performed was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

Claims 1, 2, 11, 12 and 21-36 lack an inventive step under PCT Article 33(3) as being obvious over SYNAPTIC PHARMACEUTICAL CORPORATION (WO 94/08040) in view of Cotton et al (Current Opinion in Biotechnol (1992) 3:24-30).

SYNAPTIC PHARMACEUTICAL CORPORATION teaches a method of amplifying a segment of human I1b adrenergic receptor gene comprising the steps of: a) providing a biological sample of the subject containing nucleic acids (page 55, lines 18-24), b) amplifying a segment of the gene using oligonucleotide primers, DNA polymerase and dNTPs (page 55, lines 18-35).

SYNAPTIC PHARMACEUTICAL CORPORATION teaches oligonucleotide primer pairs for the amplification of an alpha 1b adrenergic receptor which are greater in length than 15 nucleotides, which are non-crosshybridizing, which anneal to two distinct regions about 400 nucleotides apart with melting temperatures over 50 C (page 55, lines 23-37).

SYNAPTIC PHARMACEUTICAL CORPORATION further teaches methods for diagnosis of diseases related to human alpha 1 adrenergic receptors comprising nucleic acid probe techniques (page 12, lines 10-32). SYNAPTIC PHARMACEUTICAL CORPORATION expressly teaches a variety of diseases including hypertension, prostatic disorders, nasal congestions such as asthma, which are related to alterations in alpha 1 adrenergic receptor activity (page 73, line 32 to page 74, line 19).

SYNAPTIC PHARMACEUTICAL CORPORATION does not teach the broad

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

methods of mutation detection for analysis of patient samples.

Cotton teaches a variety of methods, which may initiate with PCR amplified nucleic acids (page 24, column 2), for the detection of mutations in patients (page 24, columns 1 and 2). Cotton expressly teaches allele specific amplification (page 27, column 1), allele specific oligonucleotides (page 26, column 2), PCR fingerprinting using southern blot analysis (page 26, column 2) as well as gradient gel electrophoresis and SSCP (page 25).

It would have been prima facie obvious to one of ordinary skill at the time the invention was made that the diagnostic method of SYNAPTIC PHARMACEUTICAL CORPORATION could be enhanced with the variety of PCR based methods of Cotton since Cotton states "The worker interested in detecting mutations has an increasing number of improving technologies to choose from. (page 27, column 2)". An ordinary practitioner would have been motivated to diagnose the mutation based diseases of SYNAPTIC PHARMACEUTICAL CORPORATION using any of the improving technologies of Cotton since they are useful and well defined mutation detection systems which are easy to perform.

Claims 15 and 19 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest SEQ ID NO: 7. Emorine teaches a sequence which differs from SEQ ID NO: 7 by a single nucleotide. Because this change is silent with regard to the protein structure, and was not taught in the prior art, SEQ ID NO: 7 is novel and unobvious.

Claims 1-36 meet the criteria set out in PCT Article 33(4) for industrial applicability.

---------- NEW CITATIONS ----------
NONE

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
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DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/23496

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) : C07H 21/02, 21/04; C12Q 1/68; C12P 19/34
US CL : 536/24.3, 24.31, 24.32, 24.33; 435/6, 91.1, 91.2, 91.21
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 536/24.3, 24.31, 24.32, 24.33; 435/6, 91.1, 91.2, 91.21

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,578,611 A (GLUCHOWSKI et al) 26 November 1996, see entire document.	1-36
Y	US 4,683,195 A (MULLIS et al) 28 July 1987, see entire document.	1-36
Y	US 5,556,753 A (BARD et al) 17 September 1996, see entire document.	1-36
Y, P	US 5,714,381 A (BARD et al) 03 February 1998, see entire document.	1-36
Y	WO 97/35963 A1 (DAINIPPON PHARMACEUTICAL CO.) 02 October 1997, see entire document.	1-36
Y	WO 94/08040 A1 (SYNAPTIC PHARMACEUTICAL CORPORATION) 14 April 1994, see entire document.	1-36

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 17 FEBRUARY 1999	Date of mailing of the international search report 17 MAR 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JEFFREY FREDMAN Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/23496

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95/28397 A1 (MERCK & CO., INC.) 26 October 1995, see entire document.	1-36
Y	RAMARAO et al. Genomic organization and expression of the human alpha 1B adrenergic receptor. Journal of Biological Chemistry. 25 October 1992. Vol. 267, No. 30, pages 21936-21945, see entire document.	1-36
Y	EMORINE et al. Structure of the gene for human B2 adrenergic receptor: expression and promoter characterization. Proc. Natl. Acad. Sci. USA. October 1987. Vol. 84. pages 6995-6999, see entire document.	1-36
Y	COTTON, R.G.H. Detection of mutations in DNA. Current Opinion in Biotechnology. 1992. Vol. 3. pages 24-30, see entire document.	1-36

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/23496

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

APS, MEDLINE, BIOSIS, CAPLUS, CANCERLIT
search terms: adrenergic, mutation, variation, alteration, allele, disease, asthma, hypertension, prostate, nucleic, DNA, RNA, oligonucleotide, receptor